Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

PlasmAr Study
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2. Patients and Methods (expanded)

2.1 Characteristics of the study intervention

The convalescent plasma infused volume was defined within the range of 5-10 ml/kg with an inferior limit around 400 ml for patients whose body weight was below 70 kg and a superior limit of 600 ml for those above 70 kg. Protocol´s suggested administration rate was 5-10 ml/kg/h, although the final rate could be adapted in accordance with the patient's tolerance and/or risk of volume overload. No standardized premedication was given before study infusion. For placebo administration, an equivalent amount of normal saline solution was given at the same rate observing similar clinical precautions. Patients were clinically monitored throughout the entire infusion process in order to assist and register any incidental adverse reaction.

2.2 Antibody measurement

The antibody analysis was performed with COVIDAR (Leloir Institute and CONICET - Argentina), IgG enzyme-linked immunosorbent assay (ELISA). COVIDAR test is capable of detecting specific IgG against spike (S) and receptor binding domain (RBD) antigens and has been previously validated and authorized by the Argentinian´s National Regulatory authority (ANMAT).

For qualitative detection of total IgG SARS-CoV-2 antibodies, serum samples diluted in with phosphate-buffered saline containing 0.05% Tween (PBS-T) and 0.8% casein were added to a pre coated wells with full-length trimeric Spike and RBD proteins (200 µl of a 1:50 dilution), and incubated for 1 h at 37°C. Following a washing step with PBS-T, 100 µl of diluted horseradish peroxidase (HRP)-conjugated with mouse anti-human IgG antibodies (BD pharmingen), was added to the wells and incubated for 30 min. at 37°C. Subsequently, the plates were washed with

PBS-T, and the peroxidase reaction was visualized incubating the plates with 100 µl of TMB solution for 30 min at 37°C. The reaction was stopped by adding 100 µl of 1M sulfuric acid, and optical densities (OD) were immediately measured at 450 nm.

For IgG end point titration human serum samples were initially diluted 5-folds and subsequently 2-fold serial diluted in IgG SARS-CoV-2 negative serum or fetal bovine serum (FBS). Subsequently, pre diluted serum was 10-fold diluted in PBS-T containing 0.8% casein in a final volume of 200 µl to finally continue with the protocol described above.

2.3 Data collection and clinical follow up

Demographic, comorbid conditions and concomitant medications were recorded at enrollment. REDCap was used for data collection [1]. Patients were clinically followed for a period of 30 days after enrollment. In case of earlier hospital discharge, a phone based follow up was scheduled in order to look up for clinical outcomes and adverse events until day 30, in compliance with current healthcare protection policies. During in-hospital follow up, clinical status was recorded on a daily basis, blood count/general chemistry were drawn on days 3, 7 and 14, D-Dimer and ferritin levels at day 14 and measurement of total antibody levels were performed on days 0, 2, 7 and 14 if available. Adverse events were registered and reported on an ongoing basis.

2.4 Randomization, masking and blinding

Potential study participants were screened by the study investigators for eligibility prior to randomization. A maximum lapse of 24 hours was allowed for the screening and consent process. The study did not preclude administration of another experimental treatment if reciprocal

consideration was allowed for the use of convalescent plasma. Subsequently, patients were randomly assigned through the REDCap® randomization program, in a 2:1 ratio to receive either Covid-19 convalescent plasma transfusion or placebo (normal saline solution)[1]. Randomization was performed in variable size blocks of 3, 6, 9 and 12 participants and stratified by clinical site. Randomization process was carried out by the designated unblinded investigators, who were not blinded to treatment assignment. The same unblinded staff was responsible for preparing the infusion bag with the plasma/saline content and masking both the bag and the whole infusion line with an opaque sleeve. The study statistics team was also unblinded for the purpose of elaborating interim analysis and safety reports. Both participants and the clinical research team remained blind to the treatment assignment.

2.5 Covid-19 plasma donation process

Patients with a history of SARS-CoV-2 diagnosis confirmed by RT-PCR, fully recovered from a clinical perspective and discharged from the hospital for at least 2 weeks, and were considered eligible for donation. In accordance with the current Argentinian law and regulations of blood and blood products and recommendations of the National Directorate of Blood and Blood Derivatives, eligibility criteria for plasma donation were as follows: age of 18 through 65 years, suitable for blood donation, with full clinical recovery after 28 days of Covid-19 diagnosis. Multiparous female donors must have a negative test for human leukocyte antigens (HLA) with a Luminex® assay. Transfusion-transmissible infections testing was performed in all donors at least two times, pre-donor screening and the convalescent plasma donation day. Prior to donation, a serum total antibody titer was measured in order to ensure the therapeutic potency

of the convalescent plasma. A threshold COVIDAR IgG antibody titer of 1:400 or higher was established for accepting a potential donor. Finally, free willing written informed consent must be given by the donor.

2.6 Plasma collection, processing and storage

The transfusional medicine specialist staff of each participating center collected between 400 and 1000 ml of plasma based on routine plasma collection procedures via continuous or discontinuous flow cell separators or by manual techniques approved by the National Administration of Medicines, Food and Medical Technology of Argentina (ANMAT). Plasma pools were made with the purpose of homogenizing the intervention independently of ABO compatibility, always utilizing plasma with antibody levels against A and/or B were below 1:64. Aliquots of those plasma pools were stored for further safety traceability and SARS-CoV-2 neutralizing antibody level measurements.

2.7 Sample size and statistical analysis

2.7.1 Sample size

We estimated the sample size using the method proposed by Whitehead [2]. Individual category percentages assumed in the design and given in the protocol, are shown below for the primary ordinal outcome. Estimates for the placebo group were based upon the study by Cao et al. for the standard care arm at day 14 for hospitalized adult patients with confirmed respiratory illness Covid-19 caused by SARS-CoV-2 infection [3]. In this study, approximately 52% of the patients were hospitalized without oxygen requirement or out of the hospital on day 14 as a sum of the three

better categories in the clinical ordinal scale (sum of 4- hospitalized without supplemental oxygen requirement 24%, + 5- discharged without full return to baseline physical function 28%, + 6- discharged with full return to baseline physical function 0%). We assumed that for the case of convalescent plasma recipients this percent could be increased to 66% (14 percentage points). We assumed this same proportional improvement (an odds ratio of approximately 1.8) would apply to other category cutoff points on the ordinal scale (an underlying assumption of the proportional odds model). Based upon these assumptions, the predicted percentages in each clinical category for the convalescent plasma group would be as shown in Table S1.

2.7.2 Statistical analysis

We included all randomized patients in the analysis according to the randomization arm, except for the patient who withdrew informed consent and was the only patient not receiving the assigned intervention (per protocol analysis). In all cases we used the total number of participants who contributed values. Categorical variables were presented as absolute and relative frequency in percentage. Continuous variables were summarized as mean and standard deviation (SD) or median and interquartile interval ($IQR_{25\text{-}75}$) according to the observed distribution. We applied logarithmic transformations for continuous variables with asymmetric distribution. We used Wilcoxon rank sum test to compare the distribution of continuous and logarithmic transformed variables between exposure arms.

We evaluated the association between convalescent plasma or placebo and the ordinal primary outcome, using an ordinal logistic regression model [4, 5]. We used this model to estimate a common proportional odds ratio for the ordinal categories of the primary outcome between

arms on the 7th, 14th and 30th day. The proportional odds ratio assumption was evaluated using the Brant parallel regression assumption test [6, 7].

For time to combine events including improvement of 2 categories in the ordinal outcome or hospital discharge within 30 days, we considered deaths within 30 days, as censored at day 30 as a different approach to consider death as a competing event. We used Cox proportional hazard regression model to evaluate time to death and time to clinical improvement and to estimate the Hazard Ratios (HR). We used the Kaplan Meier method to estimate the cumulative incidence as a function of time. We used Fine and Gray regression models considering death as a competing event to estimate the sub Hazard Ratios (sHR) for the association between arm of exposure and time to discharge from hospital, discharge from the ICU, complete restitution of physical functions, and start of invasive ventilatory support [8]. We used logistic regression models to estimate the Odds Ratio for the comparison of adverse events between arms. All association measures were presented with 95% confidence intervals (95% CI).

Planned subgroup analysis were performed according to: age groups, gender, time/delay from onset of symptoms to intervention, presence of comorbidities (chronic obstructive pulmonary disease, obesity, immunosuppression, diabetes, hypertension, cardiovascular disease), baseline participant antibody titer, recruiting sites and corticosteroid concomitant treatment. We presented the interaction test *p* values with the estimated Odds Ratio for each stratum.

For comparisons of secondary outcomes, we considered statistically significant p values of less than 0.05.

2.8 Interim analysis and unblinding criteria

An interim analysis of efficacy and safety was performed after the inclusion of 50% of patients in the study. The analysis was carried out by the statistical team in a non-blind manner. The rest of the research team remained blinded to the study arms distribution. In this analysis, the objective was to define if early termination criteria had been met. For this analysis, p values less than 0.003 were considered statistically significant for the efficacy analysis according to the strategy proposed by O'Brien and Fleming [9]. According to this same strategy, p values of less than 0.049 were considered statistically significant for the final efficacy analysis.

3. Results

The complete results for all remaining secondary objectives are shown in Table S2

3.1 Subgroup analysis by age

When analyzing population characteristics stratified by age, patients over 65 years old were significantly less self-reported as healthy (16.3% vs. 51.1%), less frequently obese (39.2% vs. 56.1%) and invariably more comorbid on other conditions such as hypertension (71.9% vs. 27.2%), diabetes (23.5% vs. 13.9%), chronic obstructive pulmonary disease (13.7% vs. 2.2%) and solid tumors (16.3% vs. 5%). Older patients were more frequently under treatment with angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker (ACEI/ARB2) (44.4% vs. 18.3%), non-steroidal anti-inflammatory drugs (NSAID) (24.2% vs. 7.2%) and anticoagulants (10.5% vs. 2.2%). On the stratified analysis by age, patients over 65 years old had significantly higher levels of D-dimer (846 ng/ml [IQR_{25-75} 562-1321] vs. 644 ng/ml [IQR_{25-75} 432-924], and lower levels of ferritin (690 ng/ml [IQR_{25-75} 358-1044] vs. 904 ng/ml [IQR_{25-75} 448-1650] (Table S5). A significant difference was observed between baseline total SARS-CoV-2 IgG titer upon enrollment when stratifying the whole study population at 65 years old, with a median titer of 1:100 [IQR_{25-75} 0-1:1600] in younger participants and a median titer of 0 [IQR_{25-75} 0-1:400] in elder patients.

3.2 Subgroup analysis by titer of infused antibodies

Median titer of total SARS-CoV-2 antibodies in infused convalescent plasma pools was 1:3200 [IQR_{25-75} 1:800 – 1:3200]. Analyzing the primary outcome (ordinal scale at 30 days) in relation

with the median value, the odds ratio was 0.83 (95% CI 0.45 - 1.51), and 0.99 (95% CI 0.99 - 1.00) considering the antibody titer as a continuous variable. The Hazard Ratio for improvement in at least two categories in the ordinal scale was 1.03 (95% CI 0.73 - 1.46) considering the median of the total antibody titer, and 0.99 (95% CI 0.99 - 1.00) considering the antibody titer as a continuous variable.

The median IC80 titer of the neutralizing antibody in the 125 infused convalescent plasma pools that were available for analysis was 1:300 [IQR_{25-75} 1:136-1:511]. The correlation between total and neutralizing SARS-CoV-2 specific antibody titers in infused convalescent plasma pools is shown in Fig S1.

The analysis of the primary outcome showed an odds ratio of 0.90 (95% CI 0.44 - 1.84) considering the median of the neutralizing antibody titer, and 0.99 (95% CI 0.99 - 1.00) considering the neutralizing antibody titer as a continuous variable. The Hazard ratio for improvement in at least two categories in the ordinal scale was 0.87 (95% CI 0.57 - 1.33) for the median of the neutralizing antibody titer and 0.99 (95% CI 0.99 - 1.00) considering the neutralizing antibody titer as a continuous variable. In addition, considering the quartiles analysis for both outcomes, we did not observe any evidence of dose-response effect.

3.3 Subgroup analysis by basal titer antibodies

Of the 215 patients from whom a baseline anti SARS-CoV-2 IgG antibody level could be obtained, the median titer was 1:50 [IQR_{25-75} 0-1:800] with 46.05 % of individuals having no detectable levels. A post hoc analysis of the group of patients with non-detectable antibodies at baseline (defined by a negative ELISA test) was performed showing no significant differences either in

primary outcome (OR: 0.89; 95%CI: 0.41-1.93) or in time to improvement in at least 2 categories in the ordinal clinical scale (HR: 0.85; 95%CI: 0.49-1.46) (Figures S2 and S3).

3.4 Total SARS-CoV-2 antibody titers in time

Table S3 shows the total number of patient blood samples available for analysis at different time-points and the overall results of the total SARS-CoV-2 titers.

3.5 Adverse events

A detailed analysis of all adverse events is provided in Table S4.

4. Supplementary Tables and Figures

Table S1: Predicted outcomes in each ordinal category

	Placebo	Convalescent Plasma
1- Death.	17%	10%
2- Invasive ventilatory support.	11%	7%
3- Hospitalized with supplemental oxygen requirements.	20%	16%
4- Hospitalized without supplemental oxygen requirements.	24%	25%
5- Discharged without full restoration to baseline physical functions.	28%	41%
6- Discharged with full restoration to baseline physical functions.	0%	0%

Table S2: Secondary outcomes results

Secondary Outcomes	Convalescent plasma (n=228)	Placebo (n=105)	Effect estimate (95% CI)
Clinical outcomes at day 7	**n (%)**	**n (%)**	**Odds Ratio**
Death	3 (1.3)	4 (3.8)	0.88 (0.58-1.34)
Invasive ventilatory support	53 (23.3)	21 (20)	
Hospitalized with supplemental oxygen requirements	66 (29)	34 (32.4)	
Hospitalized without supplemental oxygen requirements	57 (25)	14 (13.3)	
Discharged without full restoration to baseline physical functions*	16 (7)	4 (3.8)	
Discharged with full restoration to baseline physical functions*	33 (14.5)	28 (26.7)	
Clinical outcomes at day 14	**n (%)**	**n (%)**	**Odds Ratio**
Death	7 (3.1)	7 (6.7)	1.00 (0.65-1.55)
Invasive ventilatory support	38 (16.7)	18 (17.1)	
Hospitalized with supplemental oxygen requirements	27 (11.8)	10 (9.5)	
Hospitalized without supplemental oxygen requirements	25 (11)	7 (6.7)	
Discharged without full restoration to baseline physical functions*	24 (10.5)	11 (10.5)	
Discharged with full restoration to baseline physical functions*	107 (46.9)	52 (49.5)	
Serum D-dimer level (ng/ml) at day 14, *median (IQR) (n=179)*	999 (421-2639)	924 (390-2374)	-
Serum ferritin level (ng/ml) at day 14, *median (IQR) (n=190)*	704 (440-1327)	647 (296-1007)	-

* According to baseline status. Abbreviations: 95%CI: confidence interval.

Table S3: Total SARS-CoV-2 antibodies titer in time (days) and by intervention groups.

SARS-CoV2 total antibodies titers	Baseline	day 2	day 7	day 14
Convalescent plasma group, *median (IQR)*	1:50 (0-1:800)	1:400 (1:200-1:1600)	1:3200 (1:1600-1:6400)	1:6400 (1:3200-1:12800)
Placebo group, *median (IQR)*	1:50 (0-1:1600)	1:400 (1:50-1:3200)	1:3200 (1:1600-1:6400)	1:12800 (1:3200-1:12800)
N	215	298	240	165
p value	0.955	0.044	0.806	0.449

Day 0 is pre-treatment, day 2-7-14 after intervention. Two sided p value. Medians are compared with the Wilcoxon Rank sum test.

Table S4. Adverse events and Serious Adverse events (*), (**)

	Convalescent Plasma (n = 228)		Placebo (n=105)	
	Any Grade	**Severe (Grade 3-4)**	**Any Grade**	**Severe (grade 3-4)**
Any adverse event	153 (67.1)	40 (17.5)	66 (62.9)	21 (20)
Hyperglycemia	34 (14.9)	0	18 (17.1)	1 (1)
Sepsis	34 (14.9)	17 (7.5)	12 (11.4)	5 (4.8)
ALT/AST increased	22 (9.6)	1 (0.4)	7 (6.7)	0
Dyspnea	21 (9.2)	0	5 (4.8)	0
Fatigue	15 (6.6)	0	11 (10.5)	0
Acute kidney injury	13 (5.7)	1(0.4)	7 (6.7)	0
Fever	17 (7.5)	2 (0.9)	3 (2.9)	1 (1)
Delirium	13 (5.7)	1 (0.4)	5 (4.8)	1 (1)
Generalized muscle weakness	10 (4.4)	0	7 (6.7)	3 (2.9)
Lung infection	13 (5.7)	4 (1.8)	2 (1.9)	1 (1)
Diarrhea	9 (3.9)	0	5 (4.8)	0
Sinus bradycardia	14 (6.1)	1 (0.4)	0	0
Headache	10 (4.4)	0	2 (1.9)	0
Cough	6 (2.6)	0	4 (3.8)	0
Insomnia	6 (2.6)	0	4 (3.8)	0
Back pain	8 (3.5)	1 (0.4)	1 (1)	0
Atrial fibrillation	5 (2.2)	0	3 (2.9)	1 (1)
Hyponatremia	3 (1.3)	0	5 (4.8)	0

Skin ulceration	4 (1.8)	0	4 (3.8)	0
Pneumothorax	5 (2.2)	3 (1.3)	2 (1.9)	2 (1.9)
Constipation	3 (1.3)	0	3 (2.9)	0
Heart failure	4 (1.8)	0	2 (1.9)	0
Acute kidney injury (dialysis)	3 (1.3)	1 (0.4)	2 (1.9)	0
Anemia	4 (1.8)	2 (0.9)	1 (1)	0
Hypernatremia	4 (1.8)	0	1 (1)	0
Hypertension	4 (1.8)	0	1 (1)	0
Muscle cramp	3 (1.3)	0	2 (1.9)	0
Urinary retention	4 (1.8)	0	1 (1)	0
Urinary tract infection	3 (1.3)	1 (0.4)	2 (1.9)	0
Thromboembolic event	4 (1.8)	3 (1.3)	0	0
Vascular disorders - Other	4 (1.8)	0	0	0
Cholecystitis	2 (0.9)	1 (0.4)	1 (1)	0
Death	2 (0.9)	2 (0.9)	1 (1)	1 (1)
Depression	3 (1.3)	0	0	0
Epistaxis	1 (0.4)	0	2 (1.9)	0
Fall	2 (0.9)	0	3	0
Leucocitosis	3 (1.3)	0	0	0
Multi-organ failure	1 (0.4)	1 (0.4)	2 (1.9)	1 (1)
Myalgia	2 (0.9)	0	1 (1)	0
Phlebitis	3 (1.3)	0	0	0
Pruritus	1 (0.4)	0	2 (1.9)	0

Respiratory failure	2 (0.9)	1 (0.4)	1 (1)	1 (1)
Respiratory failure (ECMO)	3 (1.3)	2 (0.9)	0	0
Ventricular tachycardia	0	0	3 (2.9)	3 (2.9)
Vomiting	2 (0.9)	0	1 (1)	0
Ileus	3 (1.3)	0	1 (1)	0
Anxiety	1 (0.4)	0	1 (1)	0
Aphonia	2 (0.9)	0	0	0
Bullous dermatosis	2 (0.9)	0	0	0
Creatinine increased	2 (0.9)	0	0	0
Dyspepsia	2 (0.9)	0	0	0
Headache and hypertension	2 (0.9)	0	0	0
Hematoma	2 (0.9)	0	0	0
Hypoxia	2 (0.9)	2 (0.9)	1 (1)	0
Muscle weakness lower limb	2 (0.9)	0	0	0
Productive cough	1 (0.4)	0	1 (1)	0
Rash	1 (0.4)	0	1 (1)	1 (1)
Rash maculo-papular	1 (0.4)	0	1 (1)	0
Rash pustular	1 (0.4)	0	0	0
Increase in total Bilirubin	0	0	1 (1)	0
Bleeding	1 (0.4)	0	0	0
Cardiac arrest	1 (0.4)	1 (0.4)	1 (1)	0
Chest pain	1 (0.4)	0	0	0

Chest pain - cardiac	0	0	1 (1)	0
Chills and myalgias	0	0	0	0
Dehydration	1 (0.4)	1 (0.4)	0	0
Delusions	1 (0.4)	0	0	0
Dysuria	0	0	2 (1.9)	0
Dizziness	0	0	1 (1)	0
Dysarthria	1 (0.4)	0	0	0
Dyspnea	0	0	1 (1)	0
Ear pain	1 (0.4)	0	0	0
Eczema	1 (0.4)	0	0	0
Endocarditis infective	1 (0.4)	1 (0.4)	0	0
Enterocolitis	1 (0.4)	0	0	0
Eosinophilia	0	0	1 (1)	0
Eye pain	1 (0.4)	0	0	0
Facial pain	0	0	1 (1)	0
Fungemia	0	0	1 (1)	0
Fungus Lung infection	1 (0.4)	0	0	0
GI Bleeding	1 (0.4)	0	0	0
Herpes simplex reactivation	1 (0.4)	0	0	0
Hyperkalemia	0	0	1 (1)	0
Hypertriglyceridemia	1 (0.4)	0	0	0
Hypoglycemia	1 (0.4)	0	0	0
Hypophosphatemia	2 (0.9)	0	0	0

Hypotension and Dehydration	0	0	1 (1)	1 (1)
Hypothyroidism	1 (0.4)	0	0	0
Left ventricular systolic dysfunction	1 (0.4)	0	0	0
Myocardial infarction	0	0	1 (1)	1 (1)
Myocarditis	1 (0.4)	1 (0.4)	0	0
Nausea	1 (0.4)	0	0	0
Pain	0	0	1 (1)	0
Palpitations	1 (0.4)	0	0	0
Platelet count decreased	1 (0.4)	0	0	0
Psychosis	0	0	1 (1)	0
Rectal hemorrhage	1 (0.4)	0	0	0
Rhabdomyolysis	1 (0.4)	1 (0.4)	0	0
Rhinorrhea	1 (0.4)	0	0	0
Sinus tachycardia	0	1 (0.4)	1 (1)	0
Syncope	1 (0.4)	0	0	0
Toothache	1 (0.4)	0	0	0
Urinary incontinence	1 (0.4)	0	0	0
Urinary tract pain	1 (0.4)	0	0	0
Urinary urgency	1 (0.4)	0	0	0
Wheezing	1 (0.4)	0	0	0
Myalgia	1 (0.4)	0	0	0
Others	28 (12.3)	1 (0.4)	11 (10.5)	0

Serious Adverse events	54 (23.7)	36 (15.8)	19 (18.1)	15 (14.3)
Sepsis	29 (12.7)	17 (7.5)	8 (7.6)	5 (4.8)
Lung infection	11 (4.8)	4 (1.8)	2 (1.9)	1 (1)
Acute kidney injury	6 (2.6)	1 (0.4)	2 (1.9)	2 (1.9)
Pneumothorax	4 (1.8)	3 (1.3)	2 (1.9)	2 (1.9)
Sinus bradycardia	4 (1.8)	1 (0.4)	0	0
Thromboembolic event	4 (1.8)	3 (1.3)	0	0
Acute kidney injury (dialysis)	2 (0.9)	1 (0.4)	1 (1)	0
Death	2 (0.9)	2 (0.9)	1 (1)	1 (1)
Fever	3 (1.3)	0	0	0
Multi-organ failure	1 (0.4)	1 (0.4)	2 (1.9)	1 (1)
Respiratory failure	2 (0.9)	1 (0.4)	1 (1)	1 (1)
Respiratory failure (ECMO)	3 (1.3)	2 (0.9)	0	0
Ventricular tachycardia	0	0	3 (2.9)	3 (2.9)
Hypoxia	2 (0.9)	2 (0.9)	1 (1)	0
ALT/AST increased	2 (0.9)	1 (0.4)	0	0
Heart failure	1 (0.4)	0	1 (1)	0
Ileus	2 (0.9)	0	1 (1)	0
Anemia	1 (0.4)	0	0	0
Aphonia	1 (0.4)	0	0	0
Cardiac arrest	1 (0.4)	1 (0.4)	0	0
Cholecystitis	1 (0.4)	0	0	0
Dehydration	1 (0.4)	1 (0.4)	0	0

Delirium	1 (0.4)	1 (0.4)	0	0
Dyspnea	0	0	1 (1)	0
Endocarditis infective	1 (0.4)	1 (0.4)	0	0
GI Bleeding	1 (0.4)	0	0	0
Myocardial infarction	0	0	1 (1)	1 (1)
Myocarditis	1 (0.4)	1 (0.4)	0	0
Rhabdomyolysis	1 (0.4)	1 (0.4)	0	0
Urinary tract infection	1 (0.4)	1 (0.4)	0	0
Vascular disorders - Other	1 (0.4)	0	0	0
Other	1 (0.4)	0	0	0
Infusion-related adverse events	11 (4.8)	-	2 (1.9)	-
Trali	0	-	0	-
Taco	0	-	0	-
Non haemolytic febrile reaction	5 (2.2)	-	0	-
Allergic reaction	4 (1.8)	-	2 (1.9)	-
Unexplained event	1 (0.4)	-	0	-
Technical resolution event	1 (0.4)	-	0	-

*According CTCAE v5.0 classification

**Adverse events that occurred in more than 1 patient after randomization through day 30 are shown. Some patients had more than one adverse event.

Abbreviations: AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ECMO: ExtraCorporeal Membrane Oxygenation, TACO: Transfusion Associated Circulatory Overload TRALI: Transfusion Related Acute Lung Injury

Table S5: Patients characteristics stratified by age

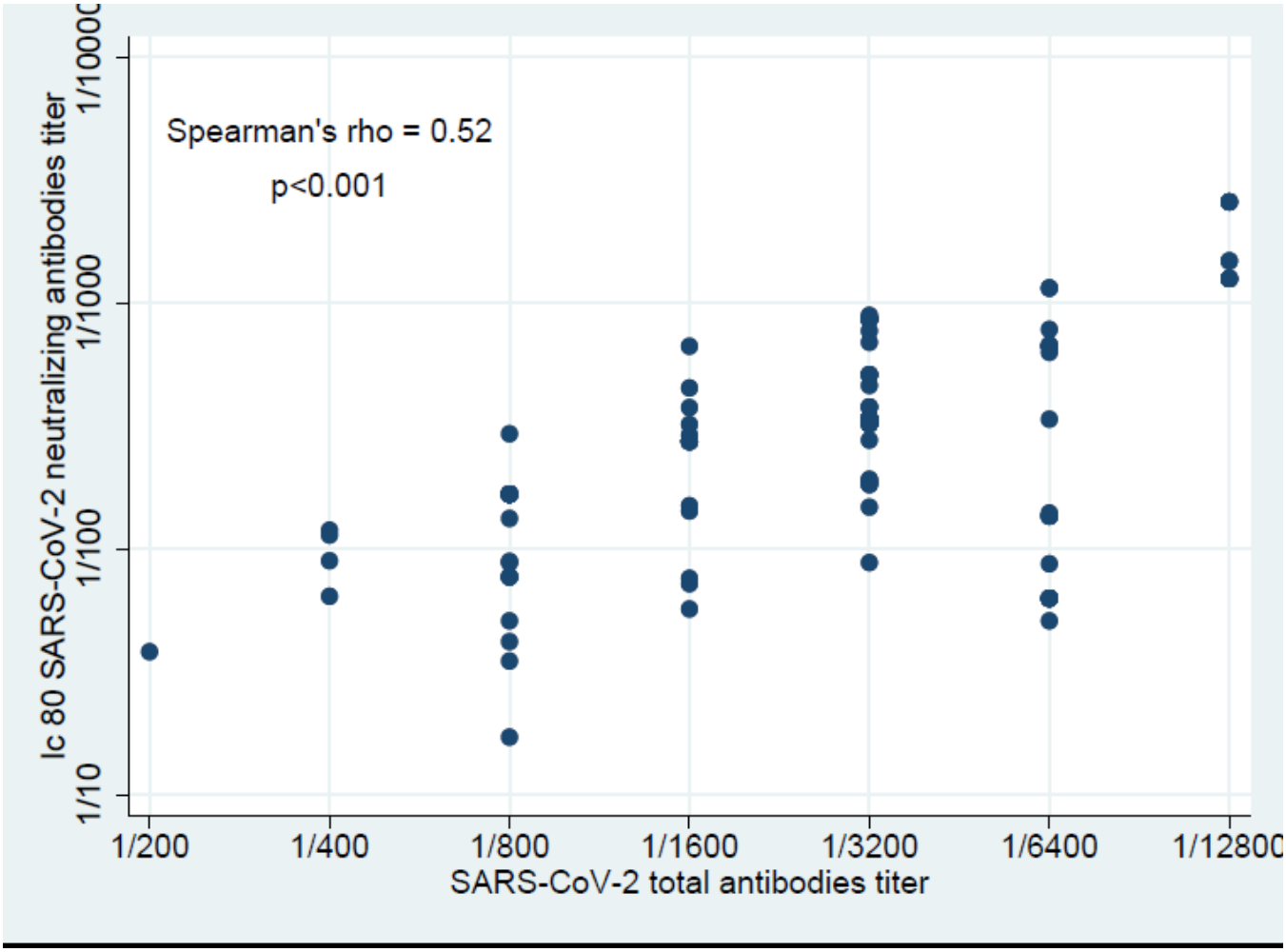
Characteristics of patients at baseline	<65 years (n=180)	≥65 years (n=153)	p value
Age (years), *median (IQR)*	53 (44.5-58)	73 (68-78)	-
Female sex, *n (%)*	54 (30)	54 (35.3)	0.304
Onset of symptoms in days, *median (IQR)*	8 (6-10)	7 (5-10)	0.099
Coexisting conditions			
No other conditions, *n (%)*	92 (51.1)	25 (16.3)	<0.001
BMI (kg/m2) over 30, *n (%)*	97 (55.1)	59 (38.8)	0.003
Hypertension, *n (%)*	49 (27.2)	110 (71.9)	<0.001
Diabetes, *n (%)*	25 (13.9)	36 (23.5)	0.023
Chronic obstructive pulmonary disease, *n (%)*	4 (2.2)	21 (13.7)	<0.001
Asthma, *n (%)*	9 (5)	5 (3.3)	0.433
Chronic renal failure, *n (%)*	6 (3.3)	8 (5.2)	0.390
Hematologic cancer, *n (%)*	4 (2.2)	3 (2)	0.868
Solid tumors, *n (%)*	9 (5)	25 (16.3)	0.001
Current tobacco use, *n (%)*	7 (3.9)	5 (3.3)	0.012
Previous tobacco use, *n (%)*	61 (33.9)	77 (50.3)	0.012
Congestive heart failure, *n (%)*	4 (2.2)	7 (4.6)	0.231
Thromboembolic disease, *n (%)*	4 (2.2)	3 (2)	0.868
Prior medications			
ACEI/ARB 2, *n (%)*	33 (18.3)	68 (44.4)	<0.001
Frequent/recent use of NSAID, *n (%)*	13 (7.2)	37 (24.2)	<0.001
Anticoagulation, *n (%)*	4 (2.2)	16 (10.5)	0.002
Corticosteroids, *n (%)*	6 (3.3)	3 (2)	0.441
Immunosuppressants, *n (%)*	6 (3.3)	3 (2)	0.441
Statins, *n (%)*	17 (9.4)	65 (42.5)	<0.001

Baseline laboratory values			
Baseline total SARS-CoV-2 antibody titer, *median (IQR)*	1:100 (0-1:1600)	0 (0-1:400)	0.022
Negative baseline total SARS-CoV-2 antibody titer, *n (%)* [#]	44 (38.3)	55 (55)	0.010
Baseline D-Dimer level (ng/ml), *median (IQR)*	644 (432-924)	846 (562-1321)	<0.001
Baseline Ferritin level (ng/ml), *median (IQR)*	904 (448-1650)	690 (358-1244)	0.033
Severity inclusion criteria			
Oxygen saturation < 93% at 0.21, *n (%)*	175 (97.2)	149 (97.4)	0.927
mSOFA or SOFA ≥ 2, *n (%)*	29 (16.1)	20 (13.1)	0.435
Hospitalization area at enrollment			
Emergency department, *n (%)*	7 (3.9)	7 (4.6)	0.867
General floor, *n (%)*	120 (66.7)	107 (69.9)	
Critical care units, *n (%)*	53 (29.4)	39 (25.5)	
Oxygen supplementation devices (n=299)			
Low flow nasal cannula, *n (%)*	119 (66.1)	97 (63.4)	0.075
Venturi/non rebreather mask, *n (%)*	32 (17.8)	33 (21.6)	
High flow nasal cannula, *n (%)*	15 (8.3)	3 (2)	
Noninvasive ventilatory support, *n (%)*	0	0	
Treatment during study [§]			
Glucocorticoids*, *n (%)*	168 (93.3)	142 (92.8)	0.851
Lopinavir-ritonavir, *n (%)*	4 (2.2)	6 (3.9)	0.522
Tocilizumab, *n (%)*	10 (5.6)	4 (2.6)	0.183
Ivermectin, *n (%)*	4 (2.2)	1 (0.7)	0.380
Hydroxychloroquine, *n (%)*	1 (0.6)	0	1.000
Adverse events			
Any adverse events, *n (%)*	108 (60)	111 (72.6)	0.016
Serious Adverse events, *n (%)*	24 (13.3)	49 (32)	<0.001

Infusion-related adverse events, *n (%)*	8 (4.6)	5 (3.3)	0.547
SARS-CoV-2 Antibodies in infused pools			
Convalescent plasma total antibodies , *median (IQR)*	1:1600 (1:800-1:3200)	1:3200 (1:1600-1:6400)	<0.001
Convalescent plasma neutralizing antibodies, *median (IQR)*	1:1023 (1:423-1:1827)	1:1143 (1:541-1:2196)	0.096

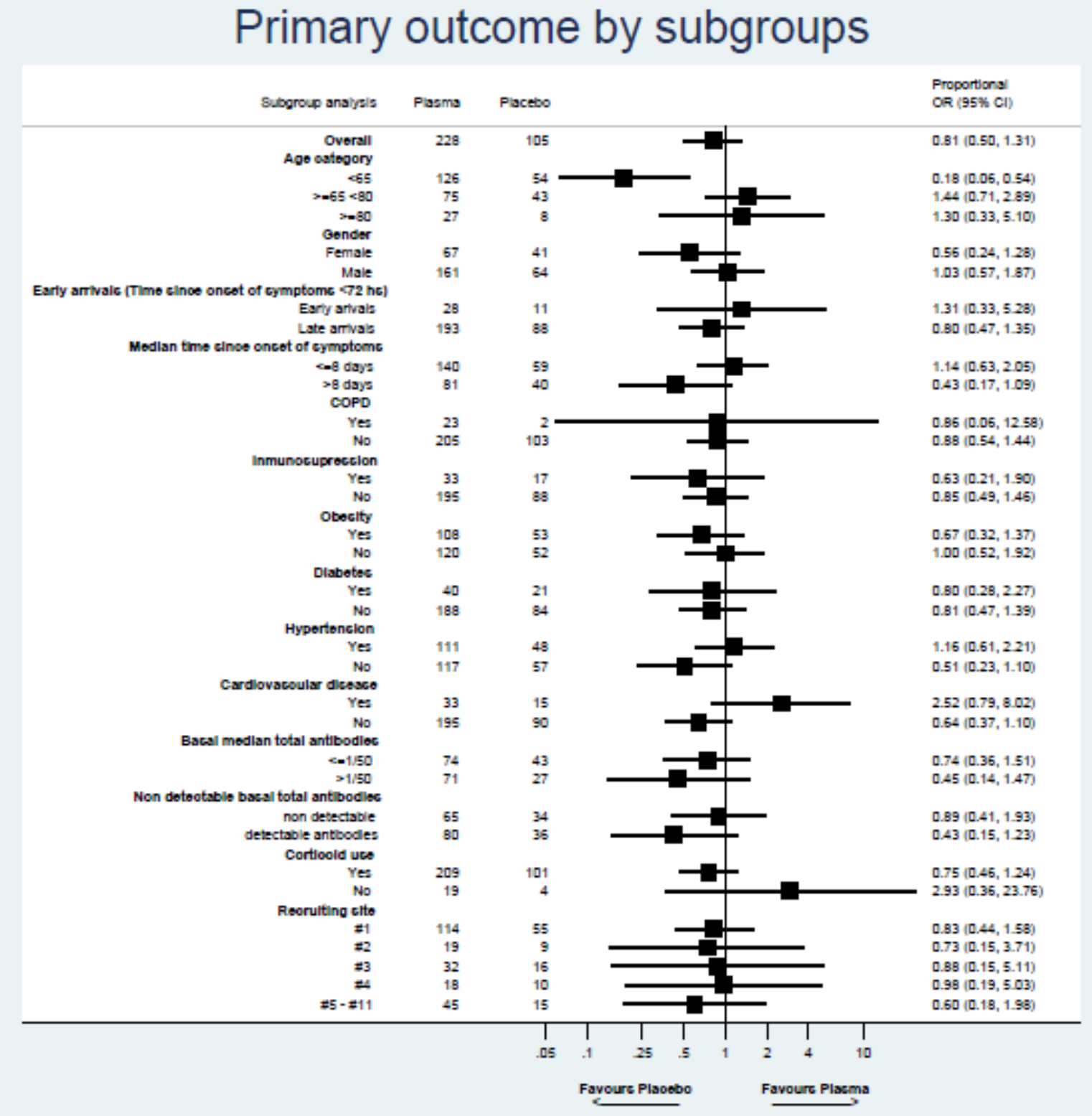
Abbreviations: BMI: body mass index, ACEI/ARB 2: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker, NSAID: non-steroidal anti-inflammatory drugs, SARS-CoV-2: severe acute respiratory syndrome- coronavirus 2, mSOFA: modified sequential organ failure assessment. # Considering 215 available samples tested, 115 in <65 years and 100 in ≥65 years. § Remdesivir was not available in Argentina during the study. *Glucocorticoids: low dose dexamethasone or equivalent doses of other corticosteroids.

Figure S1. Correlation between total and IC 80 neutralizing SARS-CoV-2 specific antibodies titers in infused convalescent plasma pools



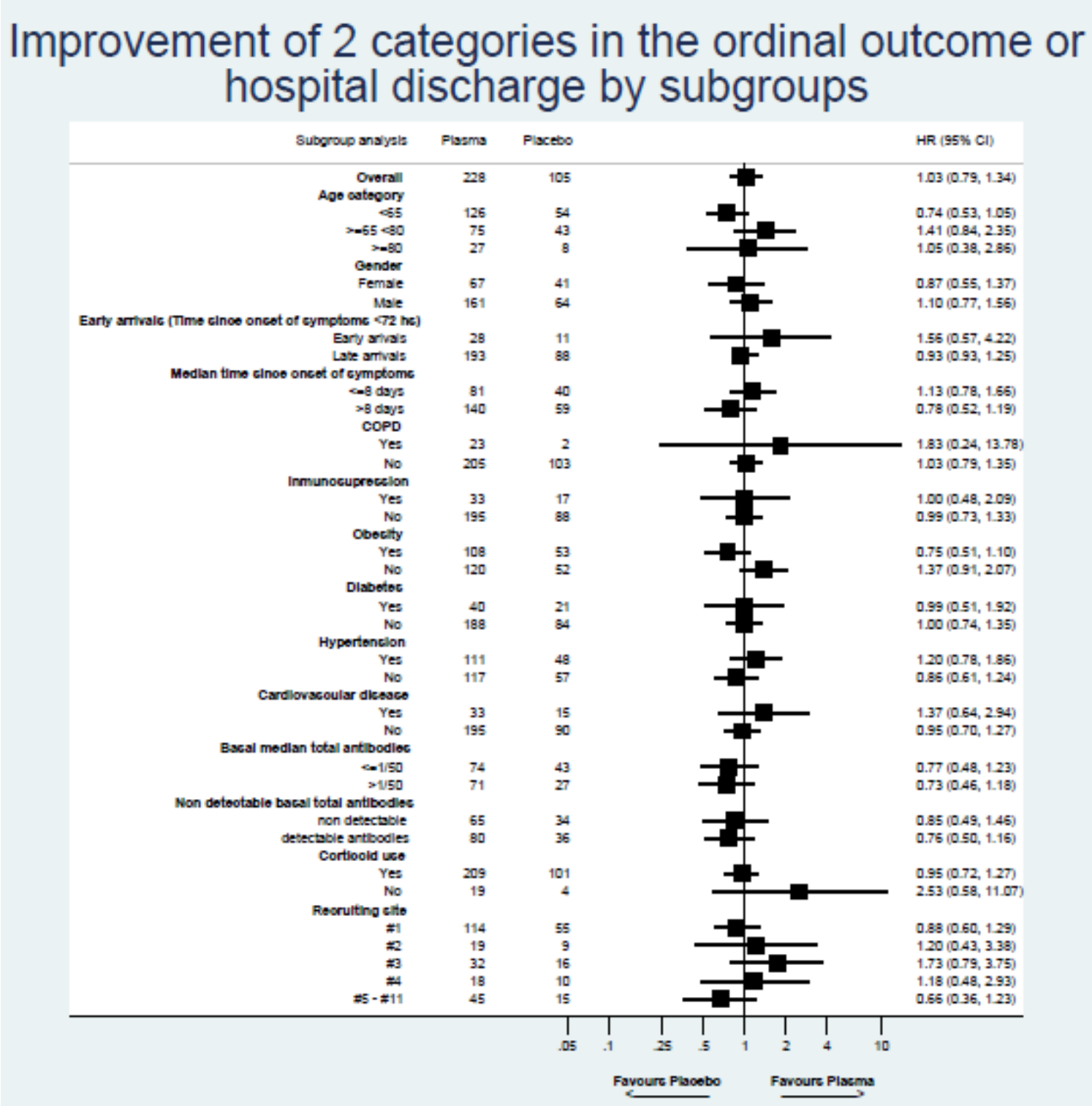
End-point IgG titrations of specific antibodies against spike and RBD were performed using the COVIDAR ELISA test. Neutralizing activity was measured through standardized replication-defective pseudotyped particle system that mimics entry of live SARS-CoV-2, as previously described [10]

Figure S2: Forest Plot of the prespecified subgroup analysis for the primary outcome at day 30



Abbreviations: COPD: chronic obstructive pulmonary disease. Non detectable basal total antibodies criterion is defined by a negative ELISA test result.

Figure S3: Forest Plot of prespecified subgroup analysis for improvement of 2 categories in the ordinal outcome or hospital discharge.



Abbreviations: COPD: chronic obstructive pulmonary disease. Non detectable basal total antibodies criterion is defined by a negative ELISA test result.

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